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10/521,313	01/14/2005	Joon Youb Lee	Q85741	9295

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/06/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/521,313	LEE ET AL.	
	Examiner	Art Unit	
	Kevin K. Hill, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *4-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 11-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *January 14, 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Applicant's response to the Requirement for Restriction, filed on February 2, 2007 is acknowledged.

Within Group I, Applicant has elected the Her-2/neu plasmid construct species "a", a Her2/neu plasmid construct, wherein the human Her-2/neu gene has the nucleotide sequence of SEQ ID NO:2, as recited in Claims 2-3

Within Group I, Applicant has elected the cytokine species "GM-CSF".

Election of Applicant's invention(s) was made without traverse. Because applicant did not distinctly and specifically point out the supposed errors in the Group or species restriction requirement, the election has been treated as an election without traverse and the restriction and election requirement is deemed proper and therefore made final (MPEP § 818).

Amendments

Applicants' amendments to Claims 1-3 and 11-16 in the reply filed February 2, 2007 is acknowledged. Also acknowledged are Applicants' new claims, Claims 17-18, which have been entered into the application as requested and will be examined on the merits herein, as they are considered to belong to the elected group, Group I.

1. Claims 4-10 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

2. Claims 1-3 and 11-18 are under consideration.

Priority

This application is a 371 of PCT/KR03/01400, filed July 15, 2003, and claims priority to KR 10-2002-0041764, filed July 15, 2002 and KR 10-2003-0038012, filed June 12, 2003.

Acknowledgment is made of Applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d).

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

A certified English translation of the parent foreign applications has not been filed. Should applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d) prior to declaration of an interference, a certified English translation of the foreign application must be submitted in reply to this action. 37 CFR 41.154(b) and 41.202(e).

Failure to provide a certified translation may result in no benefit being accorded for the non-English application.

Information Disclosure Statement

Applicant has filed Information Disclosure Statements on January 14, 2005, March 30, 2005 and December 18, 2006. These have been considered.

The information disclosure statement filed January 14, 2005 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because "(5) Each publication listed in an information disclosure statement must be identified by publisher, author (if any), title, relevant pages of the publication, date, and place of publication." It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

The Examiner acknowledges that the improperly cited references filed January 14, 2005 are properly cited in the subsequently filed IDSes of March 30, 2005 and December 18, 2006.

Some of the citations on the December 18, 2006 IDS are the same as those references properly cited on the January 14, 2005 IDS. As such, the duplicated citations on the December 18, 2006 IDS have been lined through and have been noted as duplicates ("dup"). The signed and initialed PTO Forms 1449 are mailed with this action.

Drawings

New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because the figure labels for Figures 13c, 13d, 14b and 14c contain typographical errors, specifically "challagne" should be "challenge". Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. **Claim 16 is rejected under 35 U.S.C. 112, first paragraph**, because the specification, while being enabling for a method of preventing or treating cancer in a rodent, the method(s) comprising the step of administering by intramuscular injection an effective amount of a DNA vaccine composition comprising a pTV2 vector or pCK vector which comprises a nucleotide sequence encoding a truncated human Her-2/neu protein, said truncated human Her-2/neu

protein lacking an intracellular domain, and wherein said DNA vaccine composition further comprises nucleic acid encoding the cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF), does not reasonably provide enablement for a method of preventing or treating an enormous genus of etiologically and pathologically distinct cancers in an enormous genus of mammalian subjects, including humans. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention. If not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2ds 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification. Therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention. And thus, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The Breadth of the Claims and The Nature of the Invention

With respect to the method, the claim is broad for encompassing treatment methods as applied to an enormous genus of mammals, including humans, wherein Applicant contemplates an enormous genus of DNA vaccine formulations and administration means, for example, aerosol formulation/administration, parenteral injection, suppositories, and oral formulations (pgs 9-10).

With respect to the DNA vaccine composition, the breadth of the claim is exceptionally large for encompassing a genus of structurally distinct nucleic acid compositions encoding structurally and biologically distinct polypeptides for use as a DNA vaccine for the treatment and/or prevention of an enormous genus of etiologically and pathologically distinct cancers, including carcinoma of the breast, prostate, ovary, uterus, stomach and adenocarcinoma of the lung.

When the claims are analyzed in light of the specification, the inventive concept of the instant application is to provide a DNA vaccine composition for preventing and/or treating cancer, wherein the specification discloses that Her-2/neu is amplified and over-expressed in several types of human adenocarcinomas, especially tumors of the breast and ovary. Thus, the Her-2/neu oncogene is an excellent target for the development of therapeutic vaccines specific for Her-2/neu-over-expressing human cancers (pg 1, lines 15-28).

The State of the Prior Art, The Level of One of Ordinary Skill and The Level of Predictability in the Art

Her-2/*neu* is an oncogene coding for a transmembrane protein (p185neu) and belonging to the family of tyrosine kinase growth factor receptors. Her-2/*neu* gene amplification and consequent over expression of Her-2/*neu* receptor have been observed in a significant proportion of human cancers including carcinoma of the breast, prostate, ovary, uterus, stomach and adenocarcinoma of the lung and is intimately associated with malignant phenotype and aggressiveness of the malignancy. The relevant art of the instant invention is DNA vaccines, wherein the level of skill for an ordinary artisan is high.

DNA Vaccine

At the time of the instant application (priority date of July, 2002), limited data was available regarding DNA vaccination in humans. In the early trials, eliciting anti-tumor immunity in cancer patients using DNA vaccines has proved more difficult, and little evidence of anti-tumor immunity was demonstrated using first generation tumor antigen DNA vaccines.

DNA vaccine model represents a promising, practical and effective way to elicit immune responses against an antigen expressed by malignant cells. An issue in developing tumor DNA

vaccines is to design protocols that can be translated from murine models to large animal models and clinical human use without losing their potency (Smorlesi et al, Vaccine 24: 1766-1775, 2006, pg 1767, col. 1, ¶1). The quality of the immune response elicited by a DNA vaccine is also dependent by the procedure of DNA delivery that influences the mechanisms of DNA uptake, transgene expression, and transgene product processing. The results of tumor antigen DNA vaccine approaches might be improved by optimization of key variables such as dosage, route, vector design, and boosting strategies. Thus, the role of the DNA delivery system on the outcome of the vaccine should be considered in the elaboration of a HER2/*neu* DNA vaccine.

The efficacy of DNA vaccine against HER2/*neu* is influenced by the method of release of DNA. Smorlesi et al showed that vaccine delivery methods, e.g. intramuscular injection, electroporation, and gene gun, elicited diverse immune mechanisms that differently prevented the appearance and the development of spontaneous mammary carcinomas (Smorlesi et al; pg 1773, col. 1, ¶1). The art also recognizes that the non-obvious use of a particular promoter for required expression in the desired cell type. For example, SV40, although a relatively strong promoter in fibroblasts and epithelial cell types, may be weaker than the commonly used cytomegalovirus promoter. (Chen et al, Clinical Cancer Research 6: 4381-4388, 2000; pg 4385, col. 2).

Many of the experimental systems used to evaluate the efficacy of DNA vaccine against tumor progression suffer several drawbacks, for example, immunization of healthy animals against a subsequent challenge with tumor cells was assayed rather than treatment of a tumor-bearing animal with DNA vaccine. However, patients with established, rapidly growing tumors can have an impaired cellular and humoral immune system. Therefore, it might be difficult to activate immunological defense mechanisms by vaccination (Bernhard et al, Society for Endocrinology 9(1): 33-44, 2002; pg 40, col. 1, ¶1). Moreover, while the amount of produced antibodies only partially correlate with the outcome of vaccination, the quality of humoral response seems to be determinant for the success of vaccination. Immunized mice can develop anti-Her-2/neu antibody, as demonstrated by Western blotting, but are provided no protection from tumor progression (Chen et al; pg 4385, col. 2, lines 15-17). Therefore, it is likely that DNA vaccine against a specific tumor-associated antigen may not be sufficient by itself to prevent progression of native pre-existing tumor.

The art also recognizes that a number of concerns exist with respect to immunizing with Her-2/neu vaccines. For example, once concern is that the polyclonal humoral response generated may contain immunoglobulins that can activate the Her-2/neu receptor, as has been found with some monoclonal antibodies, and lead to increased cell growth rather than inhibition (Esserman et al, Cancer Immunol. Immunther. 47: 337-342, 1999; pg 340, col. 2, ¶3). Furthermore, it is possible that increasing the anti-Her-2/neu immunity to a level necessary to destroy cancer tissue *in vivo* may also increase levels of autoimmune reactivity against normal tissues to the point of inducing toxicity (pg 341, col. 1, lines 17-21).

Animal models

Most DNA vaccine investigations are performed in models of implanted tumors that consist of the challenge of mice with a bolus of tumor cells giving rise to a fast and unnaturally growing tumor. Furthermore, the roles of p185Her-2/neu on tumor growth and immunomodulation may be altered in tumors over-expressing rat or human p185Her-2/neu. The therapeutic response may thus depend on the type of vaccine administered as well as the cancer cells used in the animal study (Lin et al, Molecular Therapy 10(2): 290-301, 2004; pg 296, col. 1, lines 11-14). Therefore, the efficacy of Her-2/neu DNA vaccine must be tested on mouse tumor cells natively over-expressing mouse p185Her-2/neu (Lin et al, pg 291, col. 1, ¶1). The art recognizes that transgenic mice reproduce the more complex spontaneous progression of a pre-neoplastic lesion and their use provides information that may be more relevant to cancer development in humans where the tumor is initiated by the clonal expansion from a single cell *in vivo* (Smorlesi et al; pg 1767, col.s 1-2, joining ¶). For example, the *Her-2/neu* transgenic mice possess distinct kinetics of disease development that better reflect spontaneous mammary carcinogenesis and recapitulate a few features of the development of human mammary carcinoma.

Although the results using plasmid DNA vaccines against HER2 have been promising in rodent models, there are drawbacks when considering the use of plasmid DNA vaccines in humans. The major drawback to the use of plasmid DNA vaccines in humans is that, although proven to be quite effective in rodents, DNA-based vaccines have generally performed poorly in both non-human primate studies as well as in human clinical trials. Thus, until formulation and

delivery technologies are developed to increase the potency of plasmid DNA vaccines in humans, this approach is not likely to be an optimal one for human vaccines (Foy et al, Seminars in Oncology 29(3 Suppl. 11): 53-61, 2002; pg 56, col. 2, ¶1). Furthermore, the art recognizes that FVB and BALB/c mice used for testing experimental DNA vaccines may not be representative for the human scenario (Chang et al, Int. J. Cancer 111: 86-95, 2004; pg 86, col. 1, last sentence). In the case of human Her-2/neu in human patients, the artisan may not reasonably extrapolate the ability to breakdown tolerance and induce an effective immune response, as achieved in animal models, because Her-2/neu is a self-tolerated antigen widely expressed at low levels in multiple tissues in humans.

Cytokine therapy

Cytokine genes have been used in many studies to enhance the immune response to a DNA vaccine against a specific antigen. Fusion genes or co-delivery of cytokine genes can augment thé immune response and influence the immune pathway. The anti-tumor responses induced by different cytokines seemed to operate through different mechanisms. For example, cytotoxic CD8+ T cells play a major role in the IL-2-induced immune response (15), whereas CD4+ and CD8+ T cells mediate the GM-CSF anti-tumor activity (Chen et al; pg 4381, col. 2, ¶1). Although several studies have indicated that GM-CSF had a strong capacity to enhance the effects of DNA vaccines by amplifying both cellular and humoral immunity, the benefit of co-administration of cytokine genes is dependent on the nature of tumor-associated antigen and the intrinsic immunologic properties of tumor cells (Lin et al; pg 298, col. 1, ¶1).

Thus, the art recognizes significant unpredictability regarding the design of any Her-2/neu DNA vaccine, with or without combined administration of nucleic acids encoding a cytokine, to reliably prevent or treat an enormous genus of etiologically and pathologically distinct tumors in an enormous genus of mammalian organisms, including mice and humans. The art speaks to the lack of standards in animal models, the difficulties to adequately mimic the complex disease pathologies observed in humans to the animal model system, and the general inability to reliably extrapolate results achieved in the rodent system to the primate system.

The Existence of Working Examples and The Amount of Direction Provided by the Inventor

The specification teaches the tumor challenge in laboratory BALB/c mice by injection of suspended human breast carcinoma cells or murine colon adenocarcinoma cells (pg 13, lines 1-5), wherein said cells either administered subcutaneously on the flank or intravenously (pg 15, lines 29-30). Applicant contemplates an enormous genus of DNA vaccine formulations and administration means (pgs 9-10); however, only intramuscular injection is disclosed as an effective administration means of vaccination. The specification also does not teach the structural nature of the expression plasmids; merely disclosing that the pCK vector has a stronger promoter activity than pTV2 (pg 22, line 18). Furthermore, the claims reasonably embrace a pTV2Neu$_{TM}$-GMCSF bi-cistronic expression plasmid (Claims 11 and 17), yet no such plasmid is disclosed in the specification. The inventive DNA vaccines are administered either before or after the tumor challenge by intramuscular injection. The specification fails to disclose that the inventive method is capable of achieving the clinically desirable results as per spontaneous tumor formation, which is the clinically relevant condition, in any other mammal, including primates such as humans. Such guidance is important in light of the wealth of data in the art teaching the inability to predictably extrapolate the instant rodent model to humans.

The Quantity of Any Necessary Experimentation to Make or Use the Invention

Thus, the quantity of necessary experimentation to make or use the invention as claimed, based upon what is known in the art and what has been disclosed in the specification, will create an undue burden for a person of ordinary skill in the art to demonstrate that the instantly claimed DNA vaccine compositions can prevent or treat an enormous genus of etiologically and pathologically distinct cancers, as contemplated by Applicant and reasonably embraced by the claims, via the enormous genus of contemplated composition formulations and administration means because the critical and essential elements of the DNA vaccine expression plasmids are not disclosed so as to guide an artisan how to make the DNA vaccine compositions and effectively target the nucleic acid to the desired cell types so as to effect the immunological response. Furthermore, the art recognizes that the model system disclosed, wherein a bolus of tumor cells is administered to the host, does not adequately represent the clinical condition wherein a patient has any one of an enormous genus of genotypically and phenotypically distinct

cancers in any one of a multitude of physiologically and pathologically distinct organs and tissues.

In conclusion, the specification fails to provide any guidance as to how an artisan would have dealt with the art-recognized limitations of the claimed method commensurate with the scope of the claimed invention and therefore, limiting the claimed invention to a method of preventing or treating cancer in a rodent, the method(s) comprising the step of administering by intramuscular injection an effective amount of a DNA vaccine composition comprising a pTV2 vector or pCK vector which comprises a nucleotide sequence encoding a truncated human Her-2/neu protein, said truncated human Her-2/neu protein lacking an intracellular domain, and wherein said DNA vaccine composition further comprises nucleic acid encoding the cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF), is proper.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. **Claims 3 and 16 are rejected under 35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

With respect to Claim 3, it is unclear whether or not the biological deposit accession numbers recited in the parentheses are actually being claimed or provided only as an example.

The Examiner respectfully suggests amending the claim to read as follows: "The vector of claim 2, wherein the pTV2 vector is pNeu$_{TM}$ deposited at the Korean Culture Center of Microorganisms (KCCM) under the accession number KCCM-10393 and the pCK vector is pCK$_{TM}$ deposited under accession number KCCM-10396."

With respect to Claim 16, the claim recites "preventing and/or treating cancer". The specification does not define the term "preventing", thus the Examiner has interpreted the claim in light of common language and definitions.

Prevent, v.

To keep from happening or arising, especially by advance planning or action

(thefreedictionary.com/prevent, last visited March 28, 2007)

It is unclear how the method to treat cancer is to be performed when the cancer has been prevented from arising in the first place.

Correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

5. **Claims 1-3, 13 and 16 are rejected under 35 U.S.C. 102(a)** as being anticipated by Lee et al (Vaccine 21(5-6):521-531, 2003; available online October 9, 2002).

With respect to Claims 1 and 13, Lee et al teach a DNA vaccine vector encoding human Her-2/neu (pNeuTM), wherein the vector backbone is a pTV2 vector (pg 522, col. 1, DNA Expression Vectors).

With respect to Claim 2, Lee et al teach the use of the human Her-2 gene, wherein the nucleic acid encoding the Her-2/neu polypeptide lacking the intracellular domain is 100% identical to SEQ ID NO:2.

With respect to Claim 3, Lee et al teach a DNA vaccine vector encoding human Her-2/neu (pNeuTM) (pg 521, col. 2, ¶2).

With respect to Claim 16, Lee et al teach a method for preventing tumor growth, wherein laboratory BALB/c mice received three intramuscular injections of DNA vaccine prior to challenge with Her-2+ CT26 colon adenocarcinoma cells (pg 525, col. 2, Section 3.4).

Thus, Lee et al anticipate Claims 1-3, 13 and 16.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. **Claims 1-3, 13 and 16 are rejected under 35 U.S.C. 103(a)** as being obvious over Piechocki et al (J. Immunol. 167: 3367-3374, 2001), Lee et al (Biochem. Biophys. Res. Comm. 272(1): 230-235, 2000) and Lee et al (Vaccine 21(5-6):521-531, 2003; available online October 9, 2002).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C.

102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Piechocki et al teach the use of a plasmid DNA vaccine encoding a human Her-2/neu polypeptide lacking the intracellular domain. Piechocki et al teach a method of preventing tumor growth, wherein laboratory BALB/c mice received three intramuscular injections of DNA vaccine prior to challenge with Her-2+ D2F2 murine mammary tumor cells (pg 3369, col. 1, Inhibition of Tumor Growth; pg 3371, Figure 3).

Piechocki et al do not teach:

i) the use of a pTV2 or pCK vector.

However, at the time of the invention, Lee et al (2000) taught the construction of a pCK expression plasmid that is able to drive high levels of gene expression *in vivo* for therapeutic use. Lee et al teach the use of this vector to express VEGF165 in mice as an example of gene therapy (pg 233, Figure 5). Similarly, Lee et al (2002) taught a DNA vaccine vector encoding human Her-2/neu (pNeuTM; pg 521, col. 2, ¶2), wherein the vector backbone is a pTV2 vector (pg 522, col. 1, DNA Expression Vectors). Lee et al taught the use of the human Her-2 gene, wherein the nucleic acid encoding the Her-2/neu polypeptide lacking the intracellular domain is 100% identical to SEQ ID NO:2. Furthermore, Lee et al taught a method for preventing tumor growth using said pNeuTM, wherein laboratory BALB/c mice received three intramuscular injections of

the DNA vaccine prior to challenge with Her-2+ CT26 colon adenocarcinoma cells (pg 525, col. 2, Section 3.4).

It would have been obvious to one of ordinary skill in the art to substitute the expression vector of Piechocki et al with the pTV2 or pCK expression vectors as taught by Lee et al (2000, 2002) with a reasonable chance of success because the Lee et al teach the ability of such vectors for use a gene therapy vehicles, even to the point of successfully demonstrating the ability to express human Her-2/neu polypeptides lacking the intracellular domain.

An artisan would be motivated to use the expression vectors of Lee et al (2000, 2002) because Lee et al teach that, for example, the newly developed pCK vector efficiently expressed the exogenously added gene *in vivo*, and reproducibly produced much higher levels of the target polypeptide than all expression vectors tested so far, including commercially available HCMV IE promoter-based plasmids and those using housekeeping gene promoters. Expression of the heterologous polypeptide lasted at least up to 16 days following a single injection. Furthermore, Lee et al suggest that pCK provides clear advantages over other previously developed plasmids, and would not only significantly increase therapeutic effects at a given dose, but also lower the costs of production, and thus treatment. With respect to the broad applicability for *in vivo* gene therapy, Lee et al anticipate the vector should be useful for gene therapy for any disease that can be treated with a reasonable level of gene expression in a transient manner in a localized area (pg 234, Discussion).

Thus, the invention as a whole is *prima facie* obvious.

7. **Claims 1, 11-15 and 17-18 are rejected under 35 U.S.C. 103(a)** as being obvious over Piechocki et al (2001), Lee et al (2000) and Lee et al (2002), as applied to Claims 1, 13 and 16 above, and in further view of Steinna et al (U.S. Patent No. 7,005,498 B1) and Pilon et al (J. Immunol..167: 3201-3206, 2001; *of record in IDS).

The prior cited art does not teach:

i) a DNA vaccine composition comprises a plasmid which expresses a gene encoding a cytokine,

ii) wherein the DNA vaccine vector further comprises a nucleotide sequence encoding a cytokine, or

iii) wherein said cytokine is GM-CSF.

However, at the time of the invention, Stienna et al contemplated a DNA vaccine composition comprising a nucleic acid vector encoding a human Her-2/neu polypeptide, wherein the Her-2/neu polypeptide may lack the intracellular domain (col. 24, lines 45-50; col. 31, lines 30-33; col.s 39-40; col.s 65-67, Example 2). Stienna et al also contemplated the DNA vaccine composition to comprise the cytokine GM-CSF. For example, the nucleic acid used as an immunization agent can also contain regions encoding immunomodulating substances such as the GM-CSF cytokine (col. 17, lines 24-33; col. 25, lines 52-56). Similarly, Pilon et al taught a DNA vaccine composition comprising a nucleic acid encoding a human Her-2/neu polypeptide, wherein the composition further comprised a plasmid expressing the GM-CSF cytokine (pg 3201, col. 2, ¶2; pg 3202, col. 1, DNA immunization).

It would have been obvious to one of ordinary skill in the art to use a DNA vaccine composition comprising a nucleic acid encoding a cytokine, e.g. GM-CSF, with a reasonable chance of success because the art has long recognized the effectiveness of vaccination to utilize various cytokines, e.g. GM-CSF, and co-stimulatory molecules as molecular adjuvants to evoke a tumor-specific CTL response. (Stienna et al, col. 4, lines 8-10).

An artisan would be motivated to use a DNA vaccine composition comprising a nucleic acid encoding a cytokine because Pilon et al teach that without co-stimulation signals, a short-lived cytotoxic T lymphocyte (CTL) response may be induced. Co-expression of GM-CSF may recruit and activate antigen-presenting cells to process and present Her-2/neu epitopes for full CTL activation (pg 3205, col. 2, last ¶), and that an effective anti-tumor response was only observed when a cytokine gene was co-administered. An artisan would also be motivated to use a bicistronic DNA vaccine vector encoding an antigen and a cytokine, either as a fusion protein or through expression of a bicistronic message because the co-expression of cytokine genes with an antigen in a plasmid may increase the local microenvironment concentration of the cytokine in the vicinity of cells that express the antigen gene, which could further augment antigen-specific immunity.

Thus, the invention as a whole is *prima facie* obvious.

Conclusion

8. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036. The examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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